PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MUETING, Ann M.
MUETING, RAASCH & GEBHARDT, P.A.
P.O. Box 581415
Minneapolis, MN 55468-1415
ETATS-UNIS D'AMERIQUE

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	12.12.2000 2/12/01 3/12/01 DV
Applicant's or agent's file reference: 110.01270201	**REPLY DUE** **within 3 month(s)** from the above date of mailing
International application No.: PCT/US00/07680	International filing date *(day/month/year)*: 22/03/2000
Priority date *(day/month/year)*: 22/03/1999	
International Patent Classification (IPC) or both national classification and IPC: A61K38/06	
Applicant: REGENTS OF THE UNIVERSITY OF MINNESOTA et al.	

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☒	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☒	Certain document cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 22/07/2001.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Fayos, C

Formalities officer (incl. extension of time limits)
Hundt, D
Telephone No. +49 89 2399 8042

WRITTEN OPINION International application No. PCT/US00/07680

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the Receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-37 as originally filed

Claims, No.:

1-40 as originally filed

Drawings, sheets:

1/15-15/15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This opinion has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-40 (industrial applicability),

because:

☒ the said international application, or the said claims Nos. 1-40 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion

could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:
see separate sheet

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrialapplicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1, 4, 5, 7, 8, 32 and 38
Inventive step (IS)	Claims	1-40
Industrial applicability (IA)	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I

Basis of the opinion

1- Sequence listing pages 1-6 filed with the letter of 11.07.2000 do not form part of the application (Rule 13ter.1(f) PCT).

Re Item II

Priority

2- The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. It the later turns out that is not correct, the documents D9 and D10 cited in the international search report could become relevant.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

3- Claims 1-40 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

4- Reference is made to the following documents:

D1: US-A-5 840 691 (EVERETT JEFFREY E ET AL) 24 November 1998 (1998-11-24)

D2: YANAKA KIYOYUKI ET AL: 'Neuronal protection from cerebral ischemia by synthetic fibronectin peptides to leukocyte adhesion molecules.' JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM, vol. 16, no. 6, 1996, pages 1120-1125, XP000952738 ISSN: 0271-678X cited in the application

D3: HINES KEITH L ET AL: 'Synthetic fibronectin peptides interrupt inflammatory cell infiltration in transforming growth factor beta-1 knockout mice.' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 91, no. 11, 1994, pages 5187-5191, XP002150881 1994 ISSN: 0027-8424 cited in the application

D4: MOHRI HIROSHI: 'Interaction of fibronectin with integrin receptors: Evidence by use of synthetic peptides.' PEPTIDES (TARRYTOWN), vol. 18, no. 6, 1997, pages 899-907, XP000952794 ISSN: 0196-9781

D5: LEVREY H ET AL: 'Induction of fibroblast apoptosis by soluble fibronectin peptides.' MOLECULAR BIOLOGY OF THE CELL, vol. 8, no. SUPPL., November 1997 (1997-11), page 181A XP000952737 37th Annual Meeting of the American Society for Cell Biology;Washington, D.C., USA; December 13-17, 1997 ISSN: 1059-1524

D6: HUEBSCH JOSEPH C ET AL: 'Endothelial cell interactions with synthetic peptides from the carboxyl-terminal heparin-binding domains of fibronectin.' CIRCULATION RESEARCH, vol. 77, no. 1, 1995, pages 43-53, XP000952796 ISSN: 0009-7330

D7: WO 89 01942 A (UNIV MINNESOTA) 9 March 1989 (1989-03-09)

D8: PROSPER FELIPE ET AL: 'Mobilization and homing of peripheral blood progenitors is related to reversible downregulation of alpha4beta1 integrin expression and function.' JOURNAL OF CLINICAL INVESTIGATION, vol. 101, no. 11, 1 June 1998 (1998-06-01), pages 2456-2467, XP002150882 ISSN: 0021-9738

D9: CHAPPELL VICKY L ET AL: 'Inhibition of leukocyte-mediated tissue destruction by synthetic fibronectin peptide (Trp-9-Tyr).' JOURNAL OF BURN CARE & REHABILITATION, vol. 20, no. 6, November 1999 (1999-11), pages 505-510, XP000952744 ISSN: 0273-8481

D10: see item VI

NOVELTY - Art. 33 (1) and (2) PCT

5- Claims 1, 4, 5, 7, 8, 32 and 38 lack novelty for the following reasons:

5.1- D1 (see e. g. c 2) relates to a method for treating conditions associated with inflammatory diseases (see c 9 lines 10-47), by administering to the patient an effective amount of a composition containing a polypeptide or mixture of polypeptides having the formula: WQPPRARI corresponding to an isolated region of fibronectin residues and capable of interacting (inhibiting) with β1-integrin.

Therefore, in the light of D1, claims 1, 4, 5, 7, 8 and 38 lack novelty.

5.2- D2 discloses the use of fibronectin peptides (Trp-Gln-Pro-Pro-Arg-Ala-Arg-Ile) (p 1121 c 2 last § - p 1122 c 1 § 1) for inhibiting the infiltration of leukocytes into ischemic tissue, reducing the size of infarction and reducing neurological dysfunction after transient focal cerebral ischemia in rats (p 1123 c 2 § 1 and p 1124 c 1 last § - c 2).

In the light of D2, claims 1, 4, 5, 7, 8 and 38 are therefore not novel.

5.3- D3 the use of fibronectin peptides (Trp-Gln-Pro-Pro-Arg-Ala-Arg-Ile - p 5188 c 1 § 3) for for blocking leukocyte recruitement and pathology in tissues (p 5187 c 2 § 3).

Hence, D3 destroys the novelty of claims 1, 4, 5, 7, 8 and 38.

6- Claims 2-3, 6, 9-32, 33-37 and 39-40 appear to be novel over the prior art cited in the search report.

6.1- The novel features are

- The β1-integrin inhibitor is a peptide comprising a C-terminal LipAr motif,
- the use of a β1-integrin inhibitor for treating burn/burn-type injuries,
- the use of a β1-integrin inhibitor for treating cancer,
- the use of a β1-integrin inhibitor for treating osteoporosis, and

- the use of a β1-integrin inhibitor for peripheralizing stem cells.

INVENTIVE STEP - Art. 33 (1) and (3) PCT

7- The problem posed in the present application is to provide means for inhibiting integrin activity in pathological conditions.

The solution proposed in the present application is the use of a β1-integrin inhibitor.

The closest prior art is represented by D1, D2 and/or D3 which report the use of a β1-integrin inhibitor for blocking leukocyte recruitment and pathologies in tissues.

8- Claims 1-40 lack inventive step for te following reasons:

8.1- The addition of a C-terminal LipAr motif to the β1-integrin inhibitor is not explicitly suggested in the available prior art. However, the addition of a C-terminal LipAr motif does not appear from the present description to provide any technical effect of the β1-integrin inhibitor in comparison with the β1-integrin inhibitor disclosed in the available prior art.

Burn and burn-type injuries are merely two of several clinical situations that share an inflammation-mediated progression of injury size and scope, and hence the use of a β1-integrin inhibitor for treating burn /burn-type injuries is not inventive since the use of β1-integrin inhibitors for treating conditions associated with inflammatory diseases is well known (see e. g. D1, D2 and/or D3).

The use of a β1-integrin inhibitor for treating cancer is suggested by e. g. D4 (see e. g. p 900 c 2 § 2 - p 901 c 1 § 3).

Osteoporosis is merely one of several clinical situations that share an inflammation-mediated progression of injury size and scope, and hence the use of a β1-integrin inhibitor for treating osteoporosis injuries is not inventive since the use of β1-integrin

inhibitors for treating conditions associated with inflammatory diseases is well known (see e. g. D1, D2 and/or D3).

The use of a β1-integrin inhibitor for peripheralizing stem cells is suggested by e. g. D8 (see e. g. discussion p 2463 - 2465).

Therefore, the subject matter of claims 1-40 lacks inventive step in the light of the prior art cited in the search report.

INDUSTRIAL APPLICABILITY - Art. 33 (1) and (4) PCT

9- For the assessment of the present claims 1-40 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

10- Certain published documents (Rule 70.10): D10

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 99/37669	29.07.99	21.01.99	22.01.98 12.08.98

Re Item VIII
Certain observations on the international application

11- The sequence numbers are missing from the claims and the description (Art. 6 PCT).

12- The subject matter of claims 25-40 (i. e. use of a β1-integrin inhibitor for the treatment of cancer, osteoporosis and for peripheralizing stem cells) is not supported by the technical contents of the description as required by Article 6 PCT.

Re Item IV
Lack of unity of invention

FOR THE SAKE OF COMPLETENESS, NOTE THAT:

13- This Authority found that the requirement of unity of invention is not complied with for the following reasons:

13.1- The common concept linking independent claims 1, 7, 13, 21, 25, 28, 32 and 35 is the use of a β1-integrin inhibitor for inhibiting integrin activity in pathological conditions. This concept is neither novel, nor inventive (see e. g. D1-D4 and D8).

13.2- Therefore, claims 1, 7, 13, 21, 25, 28, 32 and 35 are not so linked as to form a single general inventive concept (Rule 13.1 PCT) and give rise to the following separate inventions or groups of inventions:

Invention 1: A composition comprising a β1-integrin inhibitor and its use of a β1-integrin inhibitor for inhibiting inflammatory leukocyte mediated destruction of tissue (claims 1-6 and 38-40)

Invention 2: A composition comprising a β1-integrin inhibitor and its use of a β1-integrin inhibitor for treating a stroke patient (claims 7-12 and 38-40)

Invention 3: A composition comprising a β1-integrin inhibitor and its use of a β1-integrin inhibitor for treating a patient having a burn-type injury and/or a burn patient (claims 13-24 and 38-40)

Invention 4: A composition comprising a β1-integrin inhibitor and its use of a β1-integrin inhibitor for treating a cancer patient (claims 25-31 and 38-40)

Invention 5: A composition comprising a β1-integrin inhibitor and its use of a β1-integrin inhibitor for treating a patient for osteoporosis (claims 32-34 and 38-40)

Invention 6: A composition comprising a β1-integrin inhibitor and its use of a β1-integrin inhibitor for peripheralizing stem cells (claims 35-37 and 38-40)

13.3- Despite the aforementioned objection, according to Rule 68.1 PCT, this Authority has chosen not to invite the applicant to restrict the claims or pay additional fees.

14- Any information the applicant may wish to submit concerning the subject matter of the invention, should be confined to the letter of reply and not be incorporated into the application (Article 34(2)(b) PCT).

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter wether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (also rule 66.8 (a) PCT).

If the applicant regards it as appropriate, these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.
The attention of the applicant is drawn to the fact that the application may not be amended in such a way that it contains subject matter which extends beyond the content of the application as filed (Article 34(2)(b) PCT).